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Impact of Change to Existing Regulations

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Why Change?

- Manufacturing methods designed to incorporate current FDA requirements for storage and shipping of Source Plasma for manufacture:
  - Store at -20ºC or colder
  - Ship -5ºC or colder
  - Allowance for one storage temperature excursion > -20ºC but < -5ºC for less than 72 hours provided that the plasma has been and remains frozen solid
  - Provision for Source Plasma, Salvaged labeling if storage or shipping temperature does not exceed +10ºC

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Why Change?

- Final products manufactured under current storage and shipping requirements are safe and effective
  - Increased yield of plasma-derived Factor VIII is not a driver for manufacturing
  - Yield is not a regulatory issue

Considerations of Change

- Cost of new equipment
- Validation costs
- Maintenance costs
- Increased cost of plasma
- Increased cost of final products
- Employee safety considerations
- Compliance challenges

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Cost of Change

- PPTA written comments to proposed rule on labeling and storage included results of industry survey:
  - Focus in proposed rule was on -30ºC storage
  - Freezing temperature was not addressed in proposed rule
  - Survey included need/cost of equipment upgrades; validation costs; SOP/training costs; maintenance; compliance/excursion costs
- Industry estimate of cost for proposed rule was $70 million

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Current FDA Focus

- Storage temperature in proposed rule is not currently under consideration?
- Harmonization with European Pharmacopoeia Monograph discussed
  - Storage at -20ºC or below
  - For labile proteins, frozen by cooling rapidly at -30ºC or below as soon as possible and at latest within 24 hours of collection

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Issues of Freezing

- Definitional issues: What is meant by cooling rapidly?
  - Air freezing
  - Flash freezing
  - Blast freezing
  - Snap freezing
  - Shock freezing
- Which are the same? Which are different? Which are applicable to “cooling rapidly?”

Freezing Temperature

- PPTA estimates in comments to proposed rule for -30ºC storage were for air temperature freezers
- Other considerations for quick freezing methods
- Estimate per flash freezer (-55ºC) purchase, installation and service contract is approximately $90,000
  - Does not include facility/electrical system upgrades
  - Does not include increased energy consumption
  - Does not include training, SOPs, validation and other factors
  - Multiple units are needed per center

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Compliance/Cost

- Current regulations for temperature excursions and salvaged provision provide needed flexibility
- Change in freezing temperature would increase cost of plasma production: one company has estimated $2.73 per unit based on -30ºC freezing
- Changes in allowances for temperature excursions could reduce volume of plasma for use in manufacture and add compliance challenges

Trade-offs

- Resources spent in changing freezing and storage temperatures would be better utilized in today's economic environment:
  1. Infectious agent clearance research
  2. New product R and D
  3. Facility upgrades/buildouts
  4. Enhanced manufacturing technologies

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Conclusion

- Changing temperatures for freezing and storage would increase costs
- No appreciable added value for final products
- Would redirect resources that could be used for advancements/improvements
- If it isn't broken, don't fix it!